AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:45:55 ON 23 JAN 2003

=> file reg

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 14:46:03 ON 23 JAN 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 22 JAN 2003 HIGHEST RN 480390-21-4
DICTIONARY FILE UPDATES: 22 JAN 2003 HIGHEST RN 480390-21-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s sildenafil
L1 3 SILDENAFIL

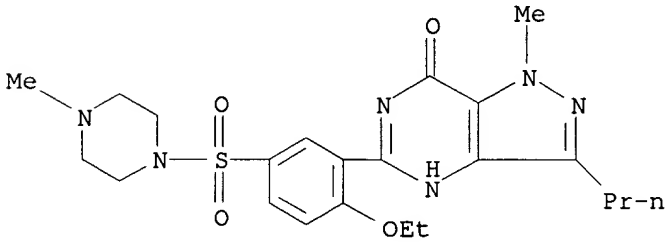
=> d 1-3

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 171599-83-0 REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)
OTHER NAMES:

CN 1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
CN **Sildenafil citrate**
CN UK 92480-10
CN Viagra
MF C22 H30 N6 O4 S . C6 H8 O7
CI COM
SR CAS Registry Services
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS, CBNB, CEN, CHEMCATS, CIN, DIOGENES, DRUGPAT, DRUGUPDATES, IPA, MRCK*, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

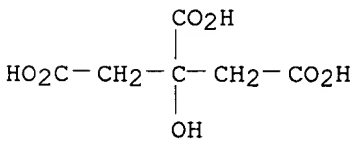
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S




CM 2

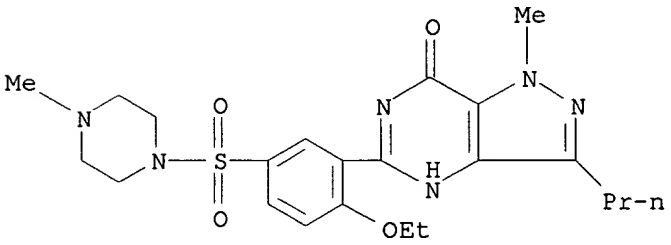
CRN 77-92-9
CMF C6 H8 O7




226 REFERENCES IN FILE CA (1962 TO DATE)
229 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 139755-83-2 REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazolo[4,3-d]pyrimidine, piperazine deriv.
OTHER NAMES:
CN 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
CN **Sildenafil**
FS 3D CONCORD
MF C22 H30 N6 O4 S

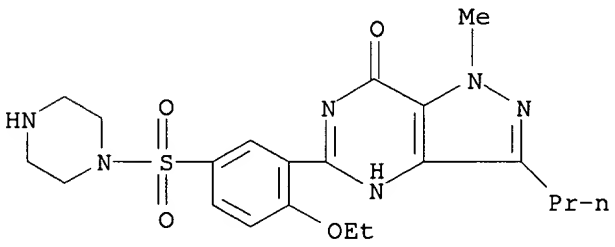
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

360 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
367 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 139755-82-1 REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazolo[4,3-d]pyrimidine, piperazine deriv.
OTHER NAMES:
CN **desmethylsildenafil**
CN UK 103320
FS 3D CONCORD
MF C21 H28 N6 O4 S
SR CA
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER, USPAT2, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

34 REFERENCES IN FILE CA (1962 TO DATE)

34 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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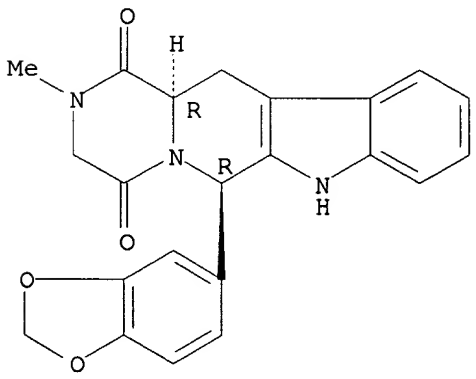
=> s ic-351
       1646994 IC
            23 ICS
       1647015 IC
                  (IC OR ICS)
          2552 351
L2           1 IC-351
                  (IC(W)351)

=> d

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   171596-29-5  REGISTRY
CN   Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-
     2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-
     2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-trans)-
OTHER NAMES:
CN   (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-
     methylenedioxyphenyl)pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione
CN   Cialis
CN   GF 196960
CN   IC 351
CN   ICOS 351
CN   Tadalafil
FS   STEREOSEARCH
DR   240822-07-5, 282541-36-0
MF   C22 H19 N3 O4
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CHEMCATS,
       CIN, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, PHAR, PROMT, SYNTHLINE,
       TOXCENTER, USAN, USPAT2, USPATFULL

Absolute stereochemistry.  Rotation (+).
```



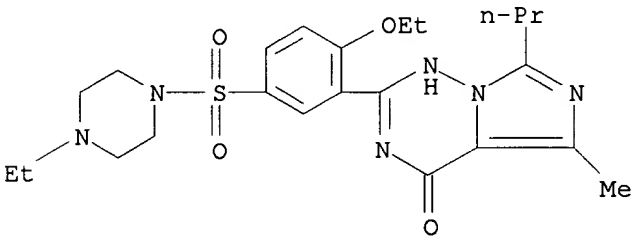

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

42 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
43 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> s vardenafil
L3 2 VARDENAFIL

=> d 1-2

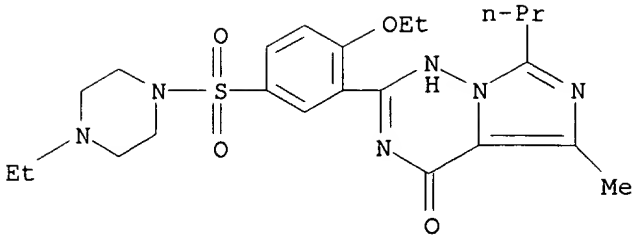
L3 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 224789-15-5 REGISTRY
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, dihydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Vardenafil dihydrochloride**
MF C23 H32 N6 O4 S . 2 Cl H
SR CA
LC STN Files: ADISINSIGHT, BIOTECHNO, CA, CAPLUS, DDFU, DRUGU, DRUGUPDATES, EMBASE, SYNTHLINE, TOXCENTER, USAN, USPATFULL
CRN (224785-90-4)




●2 HCl

5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L3 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 224785-90-4 REGISTRY
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-[2-Ethoxy-5-(4-ethylpiperazin-1-yl-1-sulfonyl)phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one
CN **Vardenafil**
FS 3D CONCORD
MF C23 H32 N6 O4 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE, PHAR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

25 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
27 REFERENCES IN FILE CAPLUS (1962 TO DATE)

```
=> s pde5 inhibitor
             6 PDE5
          8740 INHIBITOR
            10 INHIBITORS
          8749 INHIBITOR
                 (INHIBITOR OR INHIBITORS)
L4           0 PDE5 INHIBITOR
                 (PDE5(W)INHIBITOR)

=> s phosphodiesterase 5 inhibitor
          1158 PHOSPHODIESTERASE
             7 PHOSPHODIESTERASES
          1158 PHOSPHODIESTERASE
                 (PHOSPHODIESTERASE OR PHOSPHODIESTERASES)
       7885369 5
          8740 INHIBITOR
            10 INHIBITORS
          8749 INHIBITOR
                 (INHIBITOR OR INHIBITORS)
L5           0 PHOSPHODIESTERASE 5 INHIBITOR
                 (PHOSPHODIESTERASE(W)5(W)INHIBITOR)

=> s phosphodiesterase
          1158 PHOSPHODIESTERASE
             7 PHOSPHODIESTERASES
L6        1158 PHOSPHODIESTERASE
                 (PHOSPHODIESTERASE OR PHOSPHODIESTERASES)

=> s l6 and (inhibitor or antagonist)
          8740 INHIBITOR
            10 INHIBITORS
          8749 INHIBITOR
                 (INHIBITOR OR INHIBITORS)
           469 ANTAGONIST
L7           6 L6 AND (INHIBITOR OR ANTAGONIST)

=> d 1-6

L7   ANSWER 1 OF 6  REGISTRY  COPYRIGHT 2003 ACS
RN   444941-42-8  REGISTRY
CN   Guanosine cyclic 3',5'-phosphate phosphodiesterase inhibitor (mouse
     lung gene Pde6h subunit .gamma. splice isoform) (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
```

CN GenBank AF189146-derived protein GI 10441579
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L7 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 292582-10-6 REGISTRY
CN **DNA (mouse lung gene Pde6h guanosine cyclic 3',5'-phosphate phosphodiesterase inhibitor subunit .gamma. splice isoform cDNA plus 3'-flank) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF189146
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L7 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 131598-44-2 REGISTRY
CN **Phosphodiesterase, cyclic nucleotide (Dictyostelium discoideum clone pGI-1 inhibitor protein moiety reduced) (9CI)** (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA

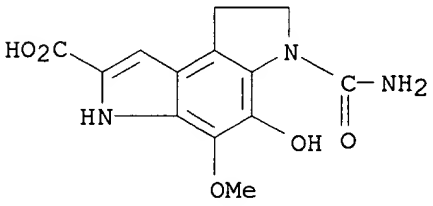
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

L7 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 131598-43-1 REGISTRY
CN **Phosphodiesterase, cyclic nucleotide (Dictyostelium discoideum clone pGI-1 inhibitor precursor protein moiety reduced) (9CI)** (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L7 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 62497-62-5 REGISTRY
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 6-(aminocarbonyl)-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy- (9CI) (CA INDEX NAME)

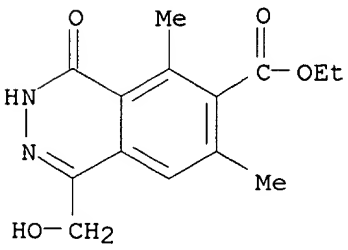
OTHER NAMES:
CN K 12
CN **K 12 (phosphodiesterase inhibitor)**
CN PDE I
FS 3D CONCORD
MF C13 H13 N3 O5
LC STN Files: ADISNEWS, BEILSTEIN*, BIOBUSINESS, CA, CAPLUS, CASREACT, DDFU, DRUGU, RTECS*, TOXCENTER
(*File contains numerically searchable property data)




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

23 REFERENCES IN FILE CA (1962 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
23 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L7 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 56611-65-5 REGISTRY
CN 6-Phthalazinecarboxylic acid, 3,4-dihydro-1-(hydroxymethyl)-5,7-dimethyl-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN EG 626
CN Oxagrelate
CN Phthalazinol
CN **Phthalazinol (phosphodiesterase inhibitor)**
FS 3D CONCORD
MF C14 H16 N2 O4
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMINFORMRX, CIN, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PHAR, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

65 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

65 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        72.40      72.61

FILE 'CAPLUS' ENTERED AT 14:48:28 ON 23 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 23 Jan 2003  VOL 138 ISS 4
FILE LAST UPDATED: 22 Jan 2003  (20030122/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s uk 0028245.9/pn
L8            0 UK 0028245.9/PN
                  (UK28245/PN)

=> s boolell
              0 BOOLELL
L9            0 BOOLELL

=> s mitradev
              0 MITRADEV
L10           0 MITRADEV

=> s pde5 inhibitor
            282 PDE5
         401493 INHIBITOR
         423948 INHIBITORS
         652769 INHIBITOR
                  (INHIBITOR OR INHIBITORS)
L11         121 PDE5 INHIBITOR
                  (PDE5(W)INHIBITOR)

=> s l11 and ejaculation
           1304 EJACULATION
            227 EJACULATIONS
           1451 EJACULATION
                  (EJACULATION OR EJACULATIONS)
L12           2 L11 AND EJACULATION

=> d ibib abs 1-2

L12  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
```

ACCESSION NUMBER: 2002:659569 CAPLUS
DOCUMENT NUMBER: 137:210286
TITLE: Vardenafil
AUTHOR(S): Ormrod, Douglas; Easthope, Stephanie E.; Figgitt, David P.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs & Aging (2002), 19(3), 217-227
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Vardenafil selectively inhibits phosphodiesterase type 5 (PDE5), an enzyme which hydrolyzes cyclic guanosine monophosphate in the cavernosum tissue of the penis. Inhibition of PDE5 results in increased arterial blood flow leading to enlargement of the corpus cavernosum. Because of the increased tumescence, veins are compressed between the corpus cavernosum and the tunica albuginea, resulting in an erection. Vardenafil has a high bioavailability and is rapidly absorbed. An erection of >60% rigidity was maintained for approx. twice as long following visual stimulation in patients treated with vardenafil 10 or 20mg than in recipients of placebo. In a large, placebo-controlled trial in patients with mild to severe erectile dysfunction (ED), vardenafil 5, 10 or 20mg taken as needed over a 12-wk period significantly improved the scores in questions 3 and 4 of the International Index of Erectile Function (IIEF). The rate of successful attempts at intercourse with **ejaculation** was also significantly higher with vardenafil (71 to 75%) than in the placebo group (39.5%), and significantly more patients treated with vardenafil than placebo responded 'yes' to a Global Assessment Question (GAQ) asking if treatment had improved erections. In a 26-wk trial in 736 men with ED of varied etiologies and severity patients receiving vardenafil 5, 10 or 20mg experienced significantly improved erections with 85% of vardenafil 20mg recipients reporting improved erectile function (assessed using the GAQ) compared with 28% of placebo recipients. Treatment with vardenafil also significantly improved scores in response to questions 3 and 4 of the IIEF compared with placebo. A 12-wk trial in 452 men with ED assocd. with diabetes mellitus demonstrated that treatment with vardenafil 20mg compared with placebo significantly improved IIEF erectile function domain scores and the rate of pos. responders to the erectile improvement GAQ. Similar results were reported in a placebo-controlled trial of vardenafil 10 to 20mg involving 440 patients with ED after radical prostatectomy. Adverse events assocd. with vardenafil were those commonly assocd. with **PDE5 inhibitors**: headache, flushing, dyspepsia and rhinitis. These were mostly dose-dependent and mild to moderate in intensity.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 2 CAPLUS 
ACCESSION NUMBER: 2002:51273 CAPLUS
DOCUMENT NUMBER: 136:96099
TITLE: Treatment of male sexual dysfunction
INVENTOR(S): Naylor, Alasdair Mark; Van der Graaf, Pieter Hadewijn; Wayman, Christopher Peter
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| WO 2002003995 | A2 | 20020117 | WO 2001-IB1187 | 20010702 |
| WO 2002003995 | A3 | 20020418 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| US 2002052370 | A1 | 20020502 | US 2001-893585 | 20010628 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| GB 2000-16684 | A | 20000706 |
| GB 2000-30647 | A | 20001215 |
| GB 2001-6167 | A | 20010313 |
| GB 2001-8483 | A | 20010404 |
| US 2000-219100P | P | 20000718 |
| GB 2001-1584 | A | 20010122 |
| US 2001-274957P | P | 20010312 |

OTHER SOURCE(S): MARPAT 136:96099

AB The present invention relates to the use of neutral endopeptidase inhibitors (NEPi) and a combination of NEPi and phosphodiesterase type ( **PDE5**) **inhibitor** for the treatment of male sexual dysfunction, in particular MED.

L16 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2000:284352 SCISEARCH
THE GENUINE ARTICLE: 302CK
TITLE: Effect of **sildenafil** citrate (Viagra) on erectile dysfunction in a patient with familial amyloidotic polyneuropathy ATTR Val30Met
AUTHOR: Obayashi K; Ando Y (Reprint); Terazaki H; Yamaskita S; Nakagawa K; Nakamura M; Yamashita T; Suga M; Ishizaki T; Uchino M; Ando M
CORPORATE SOURCE: KUMAMOTO UNIV, SCH MED, DEPT LAB MED, 1-1-1 HONJO, KUMAMOTO 8600811, JAPAN (Reprint); KUMAMOTO UNIV, SCH MED, DEPT LAB MED, KUMAMOTO 8600811, JAPAN; KUMAMOTO UNIV, SCH MED, DEPT INTERNAL MED 1, KUMAMOTO 8600811, JAPAN; KUMAMOTO UNIV, GRAD SCH CLIN PHARM, DEPT PHARMACOL & THERAPEUT, KUMAMOTO 8620973, JAPAN; KUMAMOTO UNIV, SCH MED, DEPT NEUROL, KUMAMOTO 8600811, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF THE AUTONOMIC NERVOUS SYSTEM, (12 APR 2000) Vol. 80, No. 1-2, pp. 89-92.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0165-1838.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 20

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB A 34-year-old male patient with familial amyloidotic polyneuropathy (FAP) amyloidogenic transthyretin (ATTR) Valine30Methionine (Val30Met), who underwent a liver transplantation in Sweden in 1994, was treated with **sildenafil** citrate (Viagra) to ameliorate his erectile dysfunction (ED). Some clinical symptoms and the examination data for autonomic functions were improved after liver transplantation, but ED was never improved after the operation. Five years after liver transplantation, he requested a **sildenafil** citrate therapy to enhance his erectile potential. One and a half hours after the administration of 25 mg of **sildenafil** citrate, the skin surface temperature around the pelvic area increased and the penis became erect, though the postdose hemodynamic parameters did not significantly change fi om the respective baseline or predose values. He was able to have sexual intercourse, though **ejaculation** did not occur. This case report appears to suggest that **sildenafil** citrate is an effective drug to treat ED in patients with an organic impairment of the autonomic nervous system without altering systemic circulation. 

=>

16 ANSWER 2 OF 3 EMBASE - COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999036332 EMBASE

TITLE: Effects of SSRIs on sexual function: A critical review.

AUTHOR: Rosen R.C.; Lane R.M.; Menza M.

CORPORATE SOURCE: Dr. R.C. Rosen, Department of Psychiatry, UMDNJ, Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854, United States

SOURCE: Journal of Clinical Psychopharmacology, (1999) 19/1 (67-85).
Refs: 255
ISSN: 0271-0749 CODEN: JCPYDR

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Sexual problems are highly prevalent in both men and women and are affected by, among other factors, mood state, interpersonal functioning, and psychotropic medications. The incidence of antidepressant-induced sexual dysfunction is difficult to estimate because of the potentially confounding effects of the illness itself, social and interpersonal comorbidities, medication effects, and design and assessment problems in most studies. Estimates of sexual dysfunction vary from a small percentage to more than 80%. This article reviews current evidence regarding sexual side effects of selective serotonin reuptake inhibitors (SSRIs). Among the sexual side effects most commonly associated with SSRIs are delayed **ejaculation** and absent or delayed orgasm. Sexual desire (libido) and arousal difficulties are also frequently reported, although the specific association of these disorders to SSRI use has not been consistently shown. The effects of SSRIs on sexual functioning seem strongly dose-related and may vary among the group aCCOrding to serotonin and dopamine reuptake mechanisms, induction of prolactin release, anticholinergic effects, inhibition of nitric oxide synthetase, and propensity for accumulation over time. A variety of strategies have been reported in the management of SSRI-induced sexual dysfunction, including waiting for tolerance to develop, dosage reduction, drug holidays, substitution of another antidepressant drug, and various augmentation strategies with 5-hydroxytryptamine-2 (5-HT2), 5-HT3, and .alpha.2 adrenergic receptor antagonists, 5-HT(1A) and dopamine receptor agonists, and phosphodiesterase (**PDE5**) enzyme inhibitors. Sexual side effects of SSRIs should not be viewed as entirely negative; some studies have shown improved control of premature **ejaculation** in men. The impacts of sexual side effects of SSRIs on treatment compliance and on patients' quality of life are important clinical considerations.

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L24 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:241329 CAPLUS
DOCUMENT NUMBER: 136:284433
TITLE: Administration of **phosphodiesterase** inhibitors for the treatment of **premature ejaculation**
INVENTOR(S): Wilson, Leland F.; Doherty, Paul C.; Place, Virgil A.; Smith, William L.; Abdel-Hamid, Abdou Ali Ibrahim Aboubakr
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 467,094.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002037828 | A1 | 20020328 | US 2001-888250 | 20010621 |
| US 6403597 | B2 | 20020611 | | |
| US 6037346 | A | 20000314 | US 1998-181070 | 19981027 |
| WO 2003000343 | A2 | 20030103 | WO 2002-US9415 | 20020325 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1997-958816 B2 19971028
US 1998-181070 A2 19981027
US 1999-467094 A2 19991210
US 2001-888250 A 20010621

AB A method is provided for treatment of **premature ejaculation** by administration of a **phosphodiesterase** inhibitor, e.g., an inhibitor of a Type III, Type IV, or Type **V phosphodiesterase**. In a preferred embodiment, administration is on as "as needed" basis, i.e., the drug is administered immediately or several hours prior to **sexual** activity. Pharmaceutical formulations and packaged kits are also provided. Zaprinast 1.0, mannitol 1.0, microcryst. cellulose 2.0, and magnesium stearate 10 mg are blended in a suitable mixer and then compressed into sublingual tablets. Each sublingual tablet contains 10 mg zaprinast.

IT **5**-HT antagonists
(**5**-HT3; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT **5**-HT agonists
(**5**-HT4; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT **5**-HT agonists
**5**-HT antagonists
Adrenoceptor agonists
Adrenoceptor antagonists
Antidepressants
Drug delivery systems

Human
(administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Amides, biological studies
Esters, biological studies
Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Nerve
Nervous system
(adrenergic, blockers; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(aerosols; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(beads; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(buccal; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(caplets; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(capsules; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Oximes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carbamates; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(controlled-release; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(delayed release; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Alkaloids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ergot; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(granules; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(inhalants; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Cheek
(mucosa; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(mucosal; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(nasal; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(oral; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT Drug delivery systems
(parenterals; administration of **phosphodiesterase** inhibitors

for treatment of **premature ejaculation**)
IT Drug delivery systems
(pellets; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(powders; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT **Sexual** behavior
(**premature ejaculation**; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(prodrugs; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(rectal; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(solns.; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(sublingual; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(suppositories; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(suspensions; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(sustained-release; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(syrups; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(tablets; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(topical; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT Drug delivery systems
(transdermal; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT 171596-29-5, GF 196960
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GF 196960; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)
IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 51-12-7, Nialamide 51-71-8, Phenelzine 55-21-0D, Benzamide, derivs. 58-32-2, Dipyridamole 58-55-9, Theophylline, biological studies 58-74-2, Papaverine 59-63-2, Isocarboxazid 69-89-6D, Xanthine, derivs. 72-69-5, Nortriptyline 73-22-3, Tryptophan, biological studies 83-67-0, Theobromine 91-20-3D, Naphthalene, derivs. 92-52-4D, Biphenyl, derivs. 98-89-5D, Cyclohexanecarboxylic acid, derivs. 113-45-1, Methylphenidate 113-53-1, Dothiepin 120-73-0D, Purine, derivs. 138-56-7, Trimethobenzamide 155-09-9, Tranylcypromine 271-89-6D, Benzofuran, derivs. 302-40-9, Benactyzine 303-49-1, Clomipramine 315-72-0, Opipramol 438-60-8, Protriptyline 475-81-0, S-(+)-Glaucine 616-45-5D, 2-Pyrrolidinone, derivs. 739-71-9, Trimipramine 1668-19-5, Doxepin 4350-09-8, Oxitriptan 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5118-29-6, Melitracen 5560-72-5,

Iprindole 6493-05-6, Pentoxifylline 10262-69-8, Maprotiline 10321-12-7, Propizepine 11095-43-5D, Benzothiophene, derivs. 12794-10-4D, Benzodiazepine, derivs. 14028-44-5, Amoxapine 14611-51-9, Selegiline 15301-93-6, Tofenacin 17780-72-2, Clorgyline 19794-93-5, Trazodone 21730-16-5, Metapramine 23047-25-8, Lofepramine 24219-97-4, Mianserin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25905-77-5, Minaprine 26629-87-8, Oxaflozane 28822-58-4, IBMX 29218-27-7, Toloxatone 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 34911-55-2, Bupropion 35941-65-2, Butriptyline 37762-06-4, Zaprinast 42971-09-5, Vinpocetine 46817-91-8, Viloxazine 50847-11-5, Ibudilast 51022-77-6, Etazolate 52942-31-1, Etoperidone 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56433-44-4, Oxaprotiline 56611-65-5, Phthalazinol 56775-88-3, Zimeldine 57262-94-9, Setiptiline 57574-09-1, Amineptine 59729-33-8, Citalopram 59859-58-4, Femoxetine 60719-84-8, Amrinone 60762-57-4, Pirlindole 61413-54-5, Rolipram 61869-08-7, Paroxetine 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 66208-11-5, Ifoxetine 66327-51-3, Furazlocillin 66834-24-0, Cianopramine 68475-42-3, Anagrelide 70018-51-8, Quazinone 71320-77-9, Moclobemide 72714-74-0, Viqualine 72797-41-2, Tianeptine 74150-27-9, Pimobendan 76496-68-9, Levoprotiline 78033-10-0 78351-75-4 78415-72-2, Milrinone 79030-08-3D, Griseolic acid, derivs. 79617-96-2, Sertraline 79855-88-2, Trequinsin 80410-36-2, Fezolamine 81098-60-4, Cisapride 83366-66-9, Nefazodone 83863-69-8, NorCisapride 85650-52-8, Mirtazapine 86315-52-8, Isomazole 89565-68-4, Tropisetron 90182-92-6, Zacopride 90697-57-7, Motapizone 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 94192-59-3, Lixazinone 99614-02-5, Ondansetron 102670-46-2, Batanopride 106650-56-0, Sibutramine 106730-54-5, Olprinone 109889-09-0, Granisetron 112018-01-6, Bemoradan 115344-47-3, Siguazodan 115956-12-2, Dolasetron 116539-59-4, Duloxetine 119356-77-3, Dapoxetine 121588-75-8, Amesergide 139145-27-0 139755-83-2, **Sildenafil** 147676-63-9 150452-18-9 167298-74-0, Sch-51866 167298-97-7 168464-34-4 168464-60-6 171599-83-0, **Sildenafil** citrate 184147-55-5D, derivs. 212498-37-8 224157-99-7 224785-90-4, Vardenafil 330784-28-6 330784-47-9 330785-79-0 405508-89-6 405551-89-5, FR 229934

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

IT 9025-82-5, **Phosphodiesterase** 9036-21-9, **Phosphodiesterase** III 9068-52-4, **Phosphodiesterase V**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; administration of **phosphodiesterase** inhibitors for treatment of **premature ejaculation**)

L24 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:51273 CAPLUS
DOCUMENT NUMBER: 136:96099
TITLE: Treatment of male **sexual** dysfunction
INVENTOR(S): Naylor, Alasdair Mark; Van der Graaf, Pieter Hadewijn; Wayman, Christopher Peter
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

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|---|---|---|---|---|---|
| WO 2002003995 | A2 | 20020117 | WO 2001-IB1187 | 20010702 | |
| WO 2002003995 | A3 | 20020418 | | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| US 2002052370 | A1 | 20020502 | US 2001-893585 | | 20010628 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| GB 2000-16684 | A | 20000706 |
| GB 2000-30647 | A | 20001215 |
| GB 2001-6167 | A | 20010313 |
| GB 2001-8483 | A | 20010404 |
| US 2000-219100P | P | 20000718 |
| GB 2001-1584 | A | 20010122 |
| US 2001-274957P | P | 20010312 |

OTHER SOURCE(S): MARPAT 136:96099

AB The present invention relates to the use of neutral endopeptidase inhibitors (NEPi) and a combination of NEPi and **phosphodiesterase** type (PDE5) inhibitor for the treatment of male **sexual** dysfunction, in particular MED.

IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (ORL1, modulators; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Neuropeptide Y receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Y5, antagonists; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Neuropeptide Y receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Y1, antagonists; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (agonists; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Endothelin receptors
Tachykinin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (antagonists; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Estrogens
RL: BSU (Biological study, unclassified); BIOL (Biological study) (antiestrogens; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Ion channel blockers
(calcium; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT **Sexual** behavior
(disorder, male; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dopamine-transporting, modulators; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT **Sexual** behavior
(**ejaculation**, disorder; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT Alkaloids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ergot; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT Anticholesteremic agents
(fibrates and statins; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT **Sexual** behavior
(impotence; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT Pituitary hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(melanocortin, agonists; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT Cannabinoid receptors
Estrogen receptors
Opioid receptors
Oxytocin receptors
Vasopressin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulators; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(norepinephrine-transporting, modulators; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin

converting enzyme)

IT Drug delivery systems
(oral; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Ion channel openers
(potassium; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT **Sexual** behavior
(**premature ejaculation**; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(serotonin-transporting, modulators; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Drug delivery systems
(tablets; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT **5**-HT agonists
**5**-HT antagonists
Angiotensin receptor antagonists
Anticoagulants
Dopamine agonists
Drug interactions
Drug screening
Opioid antagonists
Platelet aggregation inhibitors
Purinoceptor agonists
Vasodilators
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Estrogens
Opioids
Prostaglandins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT Adrenoceptor antagonists
(.alpha.-; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT 57576-52-0, Thromboxane A2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists; treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with

**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 82785-45-3, Neuropeptide Y
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; treatment of male **sexual** dysfunction using
neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(donors and agonists; treatment of male **sexual** dysfunction
using neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 128908-32-7, Melanocortin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(enhancers; treatment of male **sexual** dysfunction using
neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 9028-35-7, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, statins; treatment of male **sexual** dysfunction
using neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 9000-81-1, Acetylcholinesterase 9040-59-9, **Phosphodiesterase**
II 9068-52-4, **Phosphodiesterase V** 82707-54-8,
Neutral endopeptidase 138238-81-0, Endothelin converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; treatment of male **sexual** dysfunction using
neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 9036-21-9, **Phosphodiesterase** 8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(isoforms, inhibitors; treatment of male **sexual** dysfunction
using neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 9088-07-7, Natriuretic factor 85637-73-6, Atrial natriuretic factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulators; treatment of male **sexual** dysfunction using
neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sensitizing agents; treatment of male **sexual** dysfunction
using neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrates; treatment of male **sexual** dysfunction using
neutral endopeptidase inhibitors and their combination with
**phosphodiesterase** type **5** inhibitors and other agents
in relation to inhibition of angiotensin converting enzyme)

IT 9015-82-1, Angiotensin converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of male **sexual** dysfunction using neutral
endopeptidase inhibitors and their combination with

**phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT 337962-68-2P 337962-69-3P 337962-70-6P 337962-71-7P 337962-72-8P 337962-73-9P 337962-74-0P 388630-36-2P 388630-55-5P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT 58-22-0, Testosterone 71-58-9, Medroxyprogesterone acetate 520-85-4, Medroxyprogesterone 521-18-6, Dihydrotestosterone 37221-79-7, Vasoactive intestinal peptide 37221-79-7D, Vasoactive intestinal peptide, analogs 139755-83-2, **Sildenafil** 147676-53-7 171596-29-5, IC-351 215297-27-1 224785-90-4, Vardenafil 334826-98-1 334827-47-3 334827-59-7 335077-64-0 335077-70-8 389128-36-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT 98-10-2, Benzenesulfonamide 108-33-8, 2-Amino-**5**-methyl-1,3,4-thiadiazole 7663-77-6, N-(3-Aminopropyl)-2-pyrrolidinone 14068-53-2, 2-Amino-**5**-ethyl-1,3,4-thiadiazole 59892-44-3 118755-30-9 118755-86-5 118756-03-9 118783-85-0 118786-35-9 136834-71-4 136834-85-0 136850-24-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT 337962-78-4P 337962-79-5P 337962-80-8P 337962-81-9P 337962-83-1P 337962-84-2P 337962-91-1P 337962-93-3P 388630-52-2P 388630-83-9P 388631-26-3P 388631-29-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

IT 388630-37-3P 388630-54-4P 389083-04-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(treatment of male **sexual** dysfunction using neutral endopeptidase inhibitors and their combination with **phosphodiesterase** type **5** inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

L24 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:916407 CAPLUS
DOCUMENT NUMBER: 136:53755
TITLE: Synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction
INVENTOR(S): Garvey, David S.; Saenz de Tejada, Inigo; Earl, Richard A.; Khanapure, Subhash P.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: U.S., 117 pp., Cont.-in-part of U.S. 5,958,926. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6331543 | B1 | 20011218 | US 1999-387727 | 19990901 |
| US 5874437 | A | 19990223 | US 1996-740764 | 19961101 |
| WO 9819672 | A1 | 19980514 | WO 1997-US19870 | 19971031 |
| W: AU, CA, JP, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| US 5958926 | A | 19990928 | US 1998-145142 | 19980901 |
| US 2002019405 | A1 | 20020214 | US 2001-941691 | 20010830 |
| US 6462044 | B2 | 20021008 | | |

PRIORITY APPLN. INFO.: US 1996-740764 A2 19961101
WO 1997-US19870 A2 19971031
US 1998-145142 A2 19980901
US 1999-387727 A1 19990901

OTHER SOURCE(S): MARPAT 136:53755
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. I-**V**, derivs. thereof, and certain substituted Ph and phthalzaine derivs. were claimed [D2 = H, alkyl, D; D = NO, NO2, alkyl, acyl, phosphoryl, silyl, etc.; A1-3 comprise the other subunits of a **5**- or 6-membered monocyclic arom. ring; R8 = H, (halo)alkyl; p = 1-10; R24 = H, cyclohexyl, piperidinyl, etc., with the proviso that at least one of A1-3, J, or R24 contains T-Q or D; T = bond, O, S(O), amino; Q = NO, NO2; D1 = D or H; R37 = (hetero)aryl; R38 = H, halo, alkyl; G1 = alkyl, alkenyl or is part of a ring fused to the piperidine moiety of III; G4 = O, S; R40 = H, alkyl, haloalkyl, halo, etc.; R41 = alkyl, hydroxyalkyl, alkylcarboxy, etc.; R42 = aryl, alkylaryl, alkyloxyaryl; T1 = alkyl, oxyalkyl, thioalkyl, aminoalkyl]. Two synthetic examples were provided. E.g., the S-nitroso deriv. of the 3-mercapto-3-methylbutyric acid ester of dipyridamole (VI) was prepd. in 4 steps from dipyridamole in 3.**5**% overall yield. VI at doses of 10 and 30 .mu.M was more efficacious in relaxing phenylephrine-induced tissue contraction than was the known **phosphodiesterase** inhibitor, dipyridamole. The present invention describes novel (nitrosated/nitrosylated) **phosphodiesterase** inhibitors, and compns. contg. at least one (nitrosated/nitrosylated) **phosphodiesterase** inhibitor, and, optionally, one or more compds. that donate, transfer or release NO, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of NO, or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or preventing **sexual** dysfunctions in males and females, for enhancing **sexual** responses in males and females, and for treating or preventing diseases induced by the increased metab. of cGMP, such as hypertension, pulmonary hypertension, etc.

IT Nose
(allergic rhinitis; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Endothelin receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonist; combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Antiarteriosclerotics
(antiatherosclerotics; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Prostate gland
(benign hyperplasia; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Bronchi
(bronchitis; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Ion channel blockers
(calcium, combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Lung, disease
(chronic obstructive; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Dopamine agonists
Opioid antagonists
Vasodilators
(combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Prostaglandins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Artery
(coronary, angioplasty; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Mental disorder
(dementia; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Gastrointestinal motility
(disorder, dysmotility; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT **Sexual** behavior
(disorder, male, female; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Heart, disease
(edema; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Alkaloids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ergot, combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Kidney, disease
(failure; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)
IT Bladder
(incontinence; synthesis of nitrosated and nitrosylated (hetero)cyclic

**phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Heart, disease
(infarction; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Bladder
(obstruction; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Drug delivery systems
(oral; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Blood vessel, disease
(peripheral; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Ion channel openers
(potassium, combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Parturition
(**premature**; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Hypertension
(pulmonary; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Blood vessel, disease
(reduced patency in; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Drug delivery systems
(solns., injection; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Brain, disease
(stroke; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Antianginal agents
Antiasthmatics
Antiglaucoma agents
Antihypertensives
Cardiovascular agents
Cystic fibrosis
Dysmenorrhea
Edema
Immunodeficiency
(synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Thiols (organic), biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Drug delivery systems
(transdermal; synthesis of nitrosated and nitrosylated (hetero)cyclic

**phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Adrenoceptor antagonists
(.alpha.-, combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT Adrenoceptor antagonists
(.beta.-, combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 58-61-7, Adenosine, biological studies 37221-79-7, Vasoactive intestinal peptide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 380375-15-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 9040-59-9, Cyclic 3',**5**'-nucleotide **phosphodiesterase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 207607-73-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(intermediate; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 132035-65-5P 150450-88-7P, 4-[(1,3-Benzodioxol-**5**-ylmethyl)amino]-2,6-dichloroquinazoline 150452-01-0P, 1-[4-[(1,3-Benzodioxol-**5**-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid ethyl ester 150452-18-9P, 1-[4-[(1,3-Benzodioxol-**5**-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidine-carboxylic acid 194596-99-1P, 3-Methyl-3-(2,4,6-trimethoxyphenylmethylthio)butyric acid 207607-77-0P 207607-79-2P 207607-81-6P 207607-83-8P 380375-16-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 58-32-2, Dipyridamole 156-57-0, 2-Aminoethanethiol hydrochloride 1126-09-6, Ethyl isonipecotate 2620-50-0, Piperonylamine 20028-68-6, 2,4,6-Trichloroquinazoline 59729-24-7, 3-Mercapto-3-methylbutyric acid 61040-78-6, 2,4,6-Trimethoxybenzyl alcohol
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 7665-99-8, Cyclic guanosine 3',**5**'-monophosphate 9000-96-8, Arginase 10102-43-9, Nitric oxide, biological studies 90880-94-7, Endothelium-derived relaxing factor 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of

**sexual** dysfunction)

IT 56-85-9, L-Glutamine, biological studies 58-32-2D, Dipyridamole, nitroso derivs. 58-55-9D, Theophylline, nitroso derivs. 70-26-8, L-Ornithine 74-79-3, L-Arginine, biological studies 74-79-3D, L-Arginine, nitroso derivs. 156-86-5, L-Homoarginine 372-75-8, Citrulline 6493-05-6D, Pentoxifylline, nitroso derivs. 35135-01-4D, Benafentrine, nitroso derivs. 37762-06-4D, Zaprinast, nitroso derivs. 51209-75-7, S-Nitroso-cysteine 56577-02-7, S-Nitroso-N-acetylcysteine 57076-71-8D, Denbufylline, nitroso derivs. 57564-91-7, S-Nitrosoglutathione 59893-86-6 59893-86-6D, nitroso derivs. 61413-54-5D, Rolipram, nitroso derivs. 69592-38-7D, nitroso derivs. 69592-58-1D, nitroso derivs. 69592-59-2D, nitroso derivs. 69975-86-6D, Doxofylline, nitroso derivs. 78415-72-2D, Milrinone, nitroso derivs. 79032-48-7, S-Nitroso-N-acetylpenicillamine 81840-15-5D, Vesnarinone, nitroso derivs. 84243-58-3D, Imazodan, nitroso derivs. 84490-12-0D, Piroximone, nitroso derivs. 86798-59-6D, CI 930, nitroso derivs. 87164-90-7D, ICI 153110, nitroso derivs. 90697-57-7D, Motapizone, nitroso derivs. 94192-59-3D, Lixazinone, nitroso derivs. 98326-33-1D, MCI-154, nitroso derivs. 102669-89-6D, Saterinone, nitroso derivs. 102791-47-9D, Nanterinone, nitroso derivs. 106730-54-5D, Loprinone, nitroso derivs. 107189-96-8D, MS 857, nitroso derivs. 107767-55-5D, Albifylline, nitroso derivs. 112127-66-9D, nitroso derivs. 115344-47-3D, Siguazodan, nitroso derivs. 116666-63-8D, Posicor, nitroso derivs. 120223-04-3D, EMD 53998, nitroso derivs. 122130-63-6, S-Nitroso-captopril 132225-86-6D, WIN 62582, nitroso derivs. 139308-65-9D, Tolafentrine, nitroso derivs. 139427-42-2, S-Nitroso-homocysteine 139755-83-2D, **Sildenafil**, nitroso derivs. 141184-34-1D, Filaminast, nitroso derivs. 143343-83-3D, Toborinone, nitroso derivs. 144035-83-6D, Piclamilast, nitroso derivs. 144967-96-4D, WIN 63291, nitroso derivs. 145261-31-0D, Org 20241, nitroso derivs. 162401-32-3D, Roflumilast, nitroso derivs. 380375-18-8D, nitroso derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

IT 118-92-3D, Anthranilic acid, nitroso derivs. 137-44-0D, 2-Pyrazolin-**5**-one, nitroso derivs. 253-82-7D, Quinazoline, nitroso derivs. 289-80-5D, Pyridazine, nitroso derivs. 289-95-2D, Pyrimidine, nitroso derivs. 574-77-6D, Papaveroline, nitroso derivs. 8001-81-8D, Carboline, nitroso derivs. 37294-42-1D, Imidazoquinazoline, nitroso derivs. 150452-19-0D, E 4021, nitroso derivs. 171596-29-5D, ICOS 351, nitroso derivs. 380375-17-7D, nitroso derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic **phosphodiesterase** inhibitors used in treatment of **sexual** dysfunction)

REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 4 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2003:8476 SCISEARCH
THE GENUINE ARTICLE: 624PU
TITLE: Oral agents: First-line therapy for erectile dysfunction
AUTHOR: Brock G (Reprint)
CORPORATE SOURCE: Univ Western Ontario, Div Urol, Fac Med & Dent, 1151 Richmond St, London, ON N6A 5B8, Canada (Reprint); Univ Western Ontario, Div Urol, Fac Med & Dent, London, ON N6A 5B8, Canada
COUNTRY OF AUTHOR: Canada
SOURCE: EUROPEAN UROLOGY SUPPLEMENTS, (NOV 2002) Vol. 1, No. 8, pp. 12-18.

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 1569-9056.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 26

*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Oral agents are relatively non-invasive, reversible, readily administered and well tolerated; hence, they are emerging as first-line treatments for patients with erectile dysfunction. Two medications have been licensed in Europe: the dopamine agonist sublingual apomorphine, which influences central regulatory mechanisms, and the **phosphodiesterase** type **5** (PDE5) inhibitor **sildenafil** citrate, which affects local regulation of erectile function by potentiating the effects of nitric oxide. Two other potent, selective, reversible PDE5 inhibitors (tadalafil and vardenafil) are under regulatory review in Europe, the United States and other countries. In double-blind, placebo-controlled trials, these compounds significantly enhanced erectile function and increased the likelihood of successful **sexual** intercourse. largely irrespective of etiology or severity of erectile insufficiency. Apomorphine and PDE5 inhibitors also significantly improved scores in the erectile function, orgasmic function, intercourse satisfaction and overall satisfaction domains of the International Index of Erectile Function. Oral agents were well tolerated; adverse events were generally mild or moderate, prompting **premature** treatment discontinuation in a small minority of patients. The chief adverse effects with apomorphine were nausea and headache, and with PDE5 inhibitors, headache, dyspepsia and flushing. Because of a potential pharmacodynamic interaction between PDE5 inhibitors and nitrates or,nitric oxide donors that has been associated with hypotension, concomitant nitrate use is an absolute contraindication. However, the actual incidences of myocardial infarction in **sildenafil** and tadalafil patients are similar to those in placebo controls. (C) 2002 Published by Elsevier Science B.**V**.

# Sexual Medicine Program / Erectile Dysfunction



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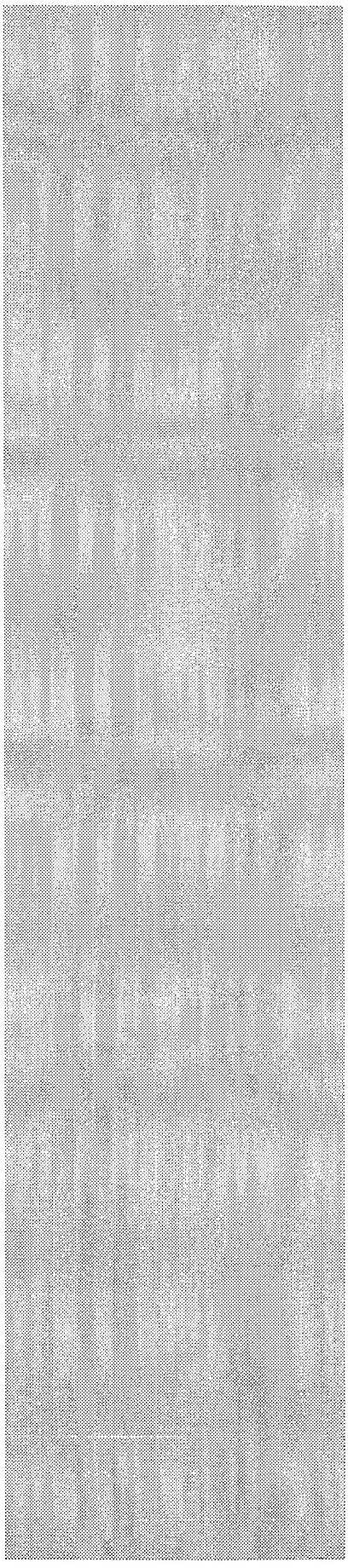
## Evaluation of the Patient with Erectile Dysfunction

The evaluation of the male with **erectile** dysfunction consists of th distinct parts, namely, **a structured interview, physical examina and adjunctive testing.** While the role of the latter is debated for general **erectile** dysfunction population, there are some patients benefit from identifying a cause of the ED. All patients presenting evaluation of impotence should undergo a comprehensive history focused physical examination. The purpose of this approach is to (1) that the patient suffers from sexual dysfunction and to determi nature of this, (2) that the patient has adequate exercise tolerance resume sexual relations, (3) that the patient does not have any co in his medical or surgical history that represent contraindications specific therapies and (4) to seek out factors in the patient's medi surgical and sexual history that may indicate an etiology of his se dysfunction.

### History

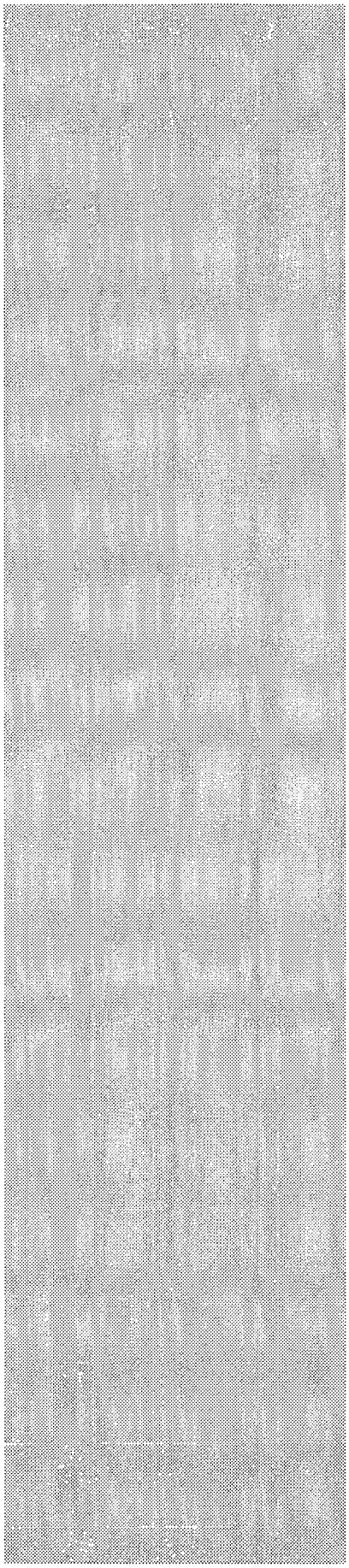
It is unknown what percentage of patients presenting to a urologis



It is unknown what percentage of patients presenting to a urologis nonsexual complaints ever get questioned regarding their sexual function. However, it has been estimated that only 30 percent of presenting to primary care physicians are asked questions regard sexual function. The reason for this is most probably multifactoria both patient and physician factors playing a role. From a patient standpoint, it is widely appreciated that embarrassment and fear p major role in a patient's reticence to broach this subject. From a p standpoint, factors interfering with initiating dialogue regarding se function include lack of physician time, lack of physician interest, physician knowledge, and cultural and religious issues.

The history taking should begin with a brief survey of the patient demographics, including his partner's age and the duration of his relationship with his partner and the specific dynamics of that rela A brief inquiry as to the female partner's menopausal status is als worthwhile. Furthermore, the dynamics in a homosexual relations different than that in a heterosexual one. History taking should the to the **medical and surgical history** of the patient. Specifically, a should be focused on vascular, neurological, endocrinological, op and psychological issues that may represent risk factors for sexua dysfunction. While urologists, internal medicine physicians, and fa practice physicians are not psychologists nor psychiatrists, a brie assessment of the patient's **psychological status** is important. Specifically, it is important to define if there are overt risk factors f psychogenic ED such as the patient being in his first relationship divorce or following being widowed, whether he is having significa interpersonal difficulties with his partner, whether he has a signifi external stressor load or the presence of an overt affective disord reference to a patient's prior surgical history, defining the time of erectile dysfunction with regard to the date of operation is import Clearly, those operations most likely to interfere with erectile fun pelvic surgeries.

Obtaining a good **medication history** is important in sexual func evaluation. Many pharmacologic agents have been associated wi erectile dysfunction, however, it is often difficult to determine whe the drug itself or the condition for which the patient is being treate the primary etiologic factor. Those medications that have been mo frequently associated with ED include anti-hypertensives, psycho medications, medications with anti-androgenic activity and recrea drugs. It is worth noting that monoamine oxidase inhibitors repres absolute contraindication to the use of systemic or intracavernosa agonist therapy. The use of recreational drugs such as marijuana cocaine, and heroine have been reported in the literature to induc erectile dysfunction. Paradoxically, cocaine is also a significant r for priapism. While the effect of cigarette smoking on systemic va is well-documented, it has not yet been clearly defined epidemiolo cigarette smoking is an *independent* risk factor for erectile dysfun The chronic use of alcohol is associated with ED through several



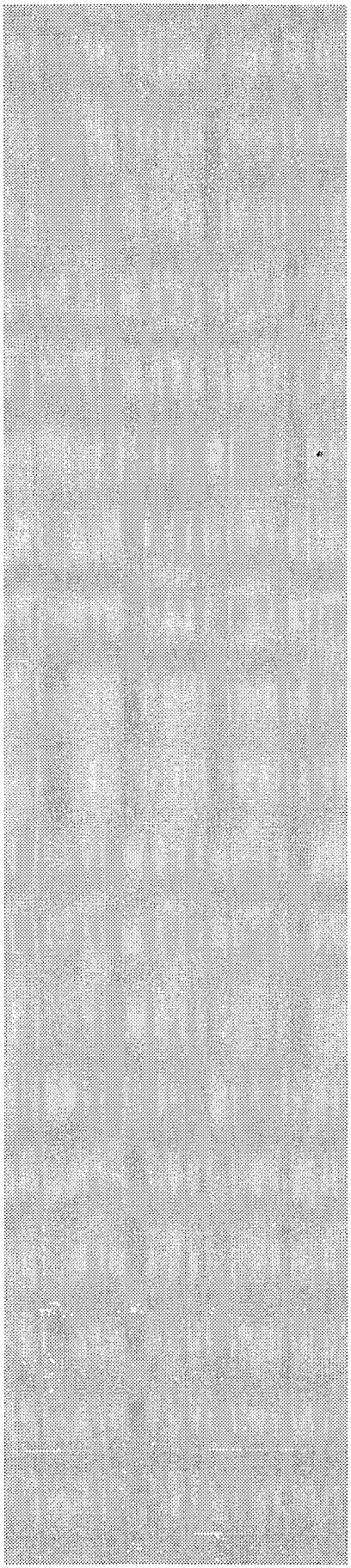
mechanisms including peripheral neuropathy, testicular dysfunctio hepatic dysfunction.

Obtaining a good **sexual history** requires practice. Firstly, it is im to define of which sexual dysfunction the patient is complaining. I uncommon for patients to confuse impotence with other sexual dysfunctions such as **premature ejaculation**, retarded orgasm, o retrograde **ejaculation**. Defining a patient's (and partner[1]s) expec and goals is also of value as some patients present purely to obta information, others[1] interest lies only in oral therapy while others w [3]whatever it takes[2] to resolve their problem.

With regard to **erectile dysfunction (ED)** the key questions inclu duration of ED, degree of ED, **erectile** spontaneity, **erectile** susta capability, early morning/nocturnal **erectile function**, timing of las intercourse, and whether the **erectile** dysfunction is situational or definition of **erectile** dysfunction is [3]the *consistent* inability to obta and/or maintain an erection sufficient for satisfactory sexual perfo therefore, consistency of ED is important. While the definition of consistency is somewhat debatable most authorities believe that with the three-month history of ED warrants treatment. Defining w the patient has primary problem with spontaneity or sustaining ca may give the clinician an idea as to the etiology of the problem. O great myths in sexual medicine is that the presence of a rigid earl morning erection indicates psychogenic ED. This is a false conce many men with significant arteriogenic ED wake up with good **ere** rigidity. The presence of good early morning erections is suggest of adequate venocclusive **function**. The hallmarks of psychogeni sudden onset **erectile** problems and intermittency of **function**, th assessing these factors by history is also important. Furthermore, if the **erectile** dysfunction is situational, such as a discrepancy in **function** between partners or between a partner and masturbatio help support a diagnosis of psychogenic ED.

Even in patients who present with **erectile** dysfunction, questions regarding **ejaculatory function, orgasmic function** and **libido** a important. The goal of the clinician should be to allow the patient to satisfactory sexual relations, and while resolution of **erectile** dysfunction is an important start, addressing and treating any sec sexual dysfunctions such as **premature ejaculation** and/or loss o will likely be necessary to maintain patient satisfaction. It is not un for patients with long-standing ED to have a significant reduction sex drive and furthermore, they are also at risk for developing **pre ejaculation** particularly if they have problems with maintenance o **erectile** rigidity. Correcting a patient's **erectile** dysfunction may h positive effect on the patient[1]s secondary **premature ejaculation**

There are a number of **validated questionnaires** available that o information regarding a patient[1]s sexual **function**. These include



International Index Of **Erectile Function** (IIEF), which is the ques routinely used at the**Sexual Medicine Program at New York Presbyterian Hospital.** More valuable to the primary care clinicia Sexual Health Inventory For Men (SHIM), a five question instrume can easily define the presence of ED. In routine clinical practice w these instruments are utilized or not is a matter of style, however, the questionnaires are used, they do not circumvent the need for face-to-face discussion as outlined above.

**PHYSICAL EXAMINATION**

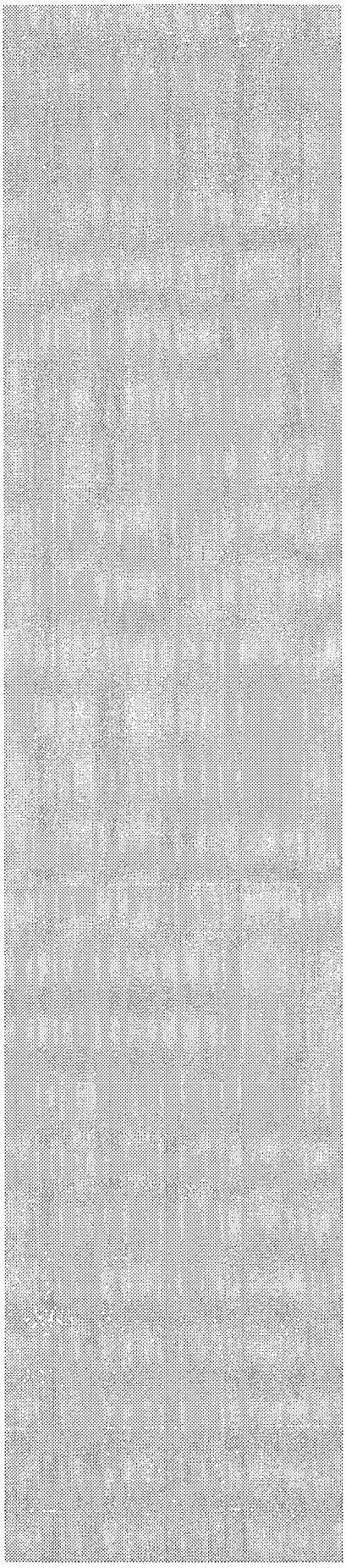
The physical examination of the patient presenting with sexual dy should focus on **(1) secondary sexual characteristics, (2) abdo examination, (3) major pulse examination, (4) S2-4 neurologic assessment, and (5) external genitalia examination.** Abdomina examination should focus on the assessment for an abdominal ao aneurysm. It has been estimated that approximately 1 percent of presenting for the evaluation of **erectile** dysfunction will have an abdominal aorta. The major pulses should be assessed, specifica femoral and popliteal pulses as these are excellent markers for sy atherosclerotic disease. In cases where there is a concern regard neurogenic ED, an assessment of S2-4 neural pathways is indica assessment of the bulbocavernosus reflex (BCR) is only of signifi benefit if the reflex is positive as 30% of neurologically intact patie have a BCR.

Examination of the penis in this patient population should focus p on the presence of Peyronie's disease plaques. A good assessme integrity of the **erectile** tissue may be gained from stretching the p shaft. In patients with significant corporal fibrosis, such as in men poorly controlled diabetes, there is significant diminishment in the of the penis to stretch, in contrast to young patients with psychog mild arteriogenic ED where penile stretch capabilities are **normal** Examination of the testicles is aimed primarily at defining the pres absence of masses and also to ascertain the testicular volume an consistency. All men over the age of 40 years and those with lowe tract symptoms undergo digital rectal examination for prostate assessment.

**Laboratory Evaluation**

Obtaining basic **hematologic and biochemistry laboratory ana** men with ED has been recommended by the NIH consensus pane screen should include **serum glucose** estimation in an effort to ru the presence of diabetes. Many of the patients seen for ED will al have had such laboratory testing by their primary care physician a not need to have this repeated. Assessment of liver **function** test thyroid **function** tests are best reserved for those patients who m symptoms and or signs suggestive of hepatic or thyroid dysfunctio

One of the great controversies in sexual medicine revolves aroun



definition of an adequate **hormonal assessment** of the patient w There is an absence of medical literature that clearly answers this question. At the **Sexual Medicine Program** at New York Presbyter Hospital a single early morning total testosterone level is drawn. Most sig endocrinopathies that are of concern will generally manifest with a low se testosterone level. In the presence of a low total testosterone level we rep blood work to include a total *and* free testosterone level, combined with a prolactin level. Most would agree that men presenting with classic symp signs of hypogonadism should undergo a full hormone screen as outlined the outset.

**Other Tests<**

In routine clinical practice the majority of men presenting with **erectile** dy do not require any further testing. However a number of investigations ex are available to aid the clinician in assigning a cause to the patient's ED. S investigations include (1) **vascular testing** such as duplex ultrasound and infusion cavernosometry/cavernosography, (2) **neurological testing** such biothesiometry, somatosensory evoked potentials and pudendal electromy and (3) **nocturnal penile tumescence and rigidity analysis.** Much deba been conducted on the indications for such investigations. In my practice, adjunctive investigations are reserved for the following groups of patients patients who are potentially curable: this group includes patients with a h for primarily psychogenic ED, patients with endocrinopathy, young males traumatically induced pure arteriogenic **erectile** dysfunction and young m isolated crural venous leak, (2) patients with penile curvature prior to und penile reconstructive surgery and (3) medicolegal cases.

There is also a significant variability in the utilization of **psychological as** during evaluation of the male with ED. Certainly, any patient who presen obvious untreated psychiatric disorder should be directed to the appropria Patients who are routinely sent for psychological evaluation and managem practice are those who have an overt complex psychological risk factor fo dysfunction and those with significant interpersonal difficulties either aris or leading to their sexual dysfunction.

Two investigations that are frequently used by clinicians in the office setti evaluation of the impotent male include **biothesiometry** and **office inject testing.** The former testing utilizes an electronic device for the assessmen vibratory thresholds. Although nomograms have been published for appro penile sensory thresholds, the value of routine biothesiometry is debated. injection testing involves the administration of intracavernosal vasoactive the ED patient and the assessment of the degree of **erectile** rigidity in res this agent. Some clinicians use this test to assess if the patient has psycho (the development of a fully rigid durable erection) or venogenic ED (failu obtain a penetration rigidity erection), however, given the fact that appro 30% of men with **normal erectile** hemodynamics will fail to obtain a pen rigidity erection in response to a single dose of intracavernosal vasoactive drawing conclusion from this test may be flawed. A positive response to t that is the development of the durable rigid erection, indicates that the pa venocclusive mechanism is intact.

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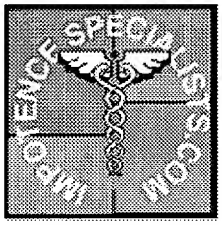


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# FAQ's

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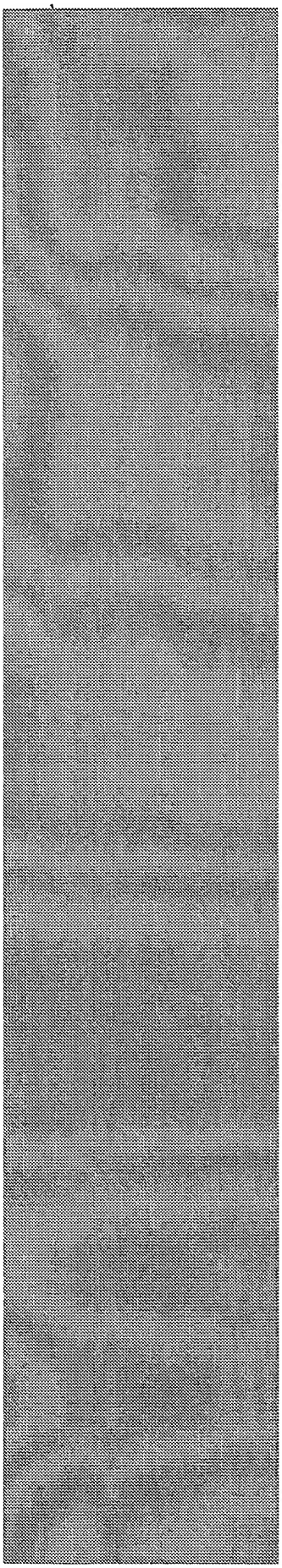
## I am not impotent. I have premature ejaculation or delayed ejaculation. What will the evaluation include?

**(more FAQ's below)**

At once time it was believed that **premature ejaculation** was completely psychologically determined. We now know that there are significant, if not **primary**, physical problems that contribute to **premature ejaculation** and it is a legitimately recognized medical problem that needs a thorough medical evaluation.

In many cases sex therapy can also be very helpful in solving this particular problem and it is sometimes recommended that patients be treated by both a physician and a sex therapist concurrently.

A first appointment should typically be between 45 and 60 minutes. It should include:
**History:** Your physician will take a thorough medical history as he will need to place your **premature ejaculation** in the context of this history. This may include questions such as:
How long do you last prior to **ejaculation**? Some men ejaculate during foreplay. Some even ejaculate while in the process of getting undressed and before significant contact



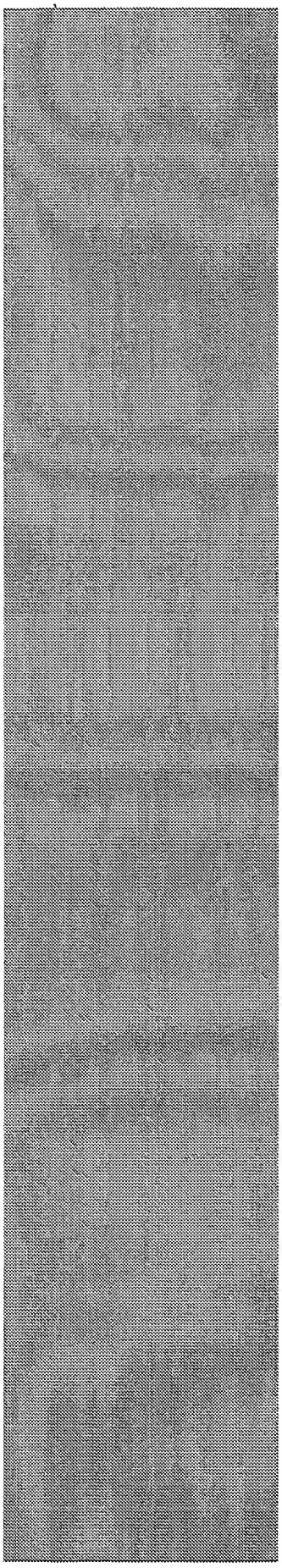
has occurred. Others penetrate, but ejaculate almost immediately with minimal thrusting. Others may last 1-5 minutes, but do ejaculate much earlier than they would like and spend most of time while inside attempting not to ejaculate.

- What is the quality of your erections?
- What happens when you try to have intercourse?
- Do you have decreased rigidity?
- Do you have difficulty maintaining your erection?
- If so, at what point do you lose it?
- Do you wake up at any point in the morning or while sleeping with an erection?
- How rigid is it then?
- What is your sexual interest level (libido) like?
- Does your penis have a curve, a bend or twist in it when it is rigid?
- Is your **ejaculation** normal?
- Is it early (**premature** or delayed)?
- He will ask you about the status of the relationship you are in. Are you married, divorced, single, gay, etc.?
- How is the relationship going?
- How is the erectile dysfunction affecting it?

If erectile dysfunction and **premature ejaculation** both exist, it is very important to determine which came first. Many men with erectile dysfunction have difficulty maintaining their erections even prior to **ejaculation**. Since they feel consciously or subconsciously pressured during intercourse to ejaculate prior to losing their erections, they can sometimes get into the habit of having **premature ejaculation**.

In general, when the erectile dysfunction preceded the **premature ejaculation**, the erectile dysfunction should be dealt with as the **primary** issue. Often when these men can achieve successful and long lasting erections they will then not ejaculate as quickly. However, if at that time the **premature ejaculation** remains a significant problem it must then be addressed separately

· *After **ejaculation**, how long does it take you to have a second erection and ability to reach an orgasm?* Some men have have had long standing **premature ejaculation** but their habit has been to ejaculate quickly (either through masturbation or with their partner) for the first **ejaculation** and then to have more leisurely intercourse as they often last longer before ejaculating the second time. Many of these men come to the physician as they get older or have



other other medical problems and lose the ability to get a rigid second erection in the same lovemaking session. At this point the **premature ejaculation** interferes significantly with their lovemaking. It is also important to know how long it takes you to get a second erection as it will be useful in determining treatment options.

· *How often do you ejaculate?* This can be either through masturbation or with a partner. Many men who develop **premature ejaculation** do not have satisfying sexual experiences. Because of this, they become somewhat avoidant of sexual situations even in the context of a relationship or marriage and have decreased frequency of intercourse and **ejaculation**. With decreased frequency and longer time periods between ejaculations many men this will ejaculate more quickly. The **premature ejaculation** can then become a vicious cycle. One of the ways of breaking the cycle is to encourage a man to ejaculate at some point prior to intercourse so that he will then last longer during intercourse.

· *How has the **premature ejaculation** effected your relationship?* Often the **premature ejaculation** is a chronic problem. For many couples, this has caused significant disturbance in their sexual relationship. Many women harbor significant resentment especially if this is a problem that the man has refused to address for a number of years. Usually a partner is very grateful that the man has sought treatment as this shows that he understands that there is a problem and that he would like to be able to satisfy his partner more completely.

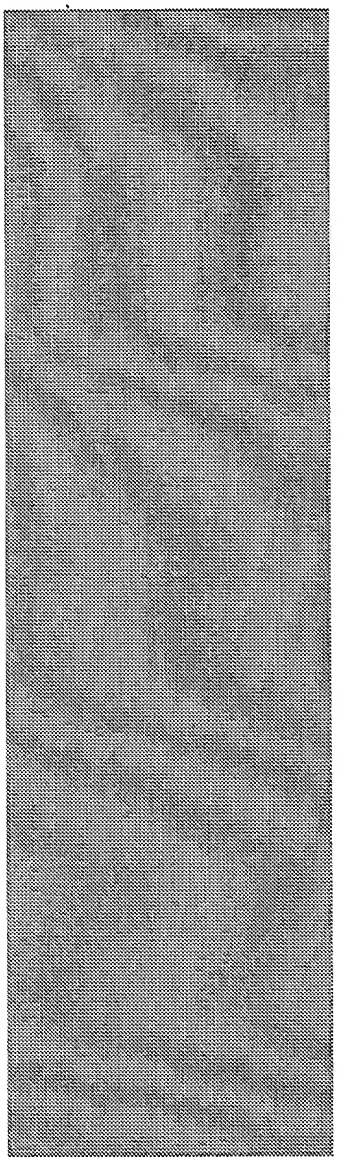
· *Have you had prior treatments?* If you have been placed on medication, it is important to know which medication and the dosage. If you have done any behavioral modifications, it is important to let the physician know this as well.

**The Physical Examination:**

Your physician will do biothesiometry to check the threshold for sensation of vibrations. Recent studies have shown that men with **premature ejaculation** have a tendency to have a decreased threshold for sensation. In other words, their penises are more sensitive. Since **ejaculation** is a reflex (one that is modified to some degree by conscious thought) these men will ejaculate more quickly as it takes much less stimulation to trigger this reflux. Your physician will also examine your penis and testes. Most physicians will draw blood for a basic hormonal screen.

**Discuss Treatment Options:**

Treatment options include behavior modification and there



are several good books available. There are also useful exercise videotapes available.

There are also medical options available. There are medications which may significantly delay your **ejaculation**, enabling you to last longer. There are also medications and treatments that may enable you to maintain your erection even after **ejaculation**. You can continue thrusting even after ejaculating and more completely satisfy your partner. Some men may ejaculate again prior to losing their erection

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ARTICLE

## Impotency/Erectile Dysfunction

**What is erectile dysfunction**
**What causes erectile dysfunction**
**How is erectile dysfunction diagnosed**
**Treatment options.**

**PRINTER F**

This document
member of the
categories:
**Andropause**
**menopause)**
**Impotency**

### What is Erectile Dysfunction?

It is the inability of a man to achieve or maintain an erection sufficient for his sexual needs or the needs of his partner. Most men experience this inability at some point in their lives, usually by age 40, and are not psychologically affected by it. Some men experience chronic, complete erectile dysfunction (impotence), and others achieve partial or brief erections. Frequent erectile dysfunction can cause emotional and relationship problems, and often leads to diminished self-esteem. It has many causes, most of which are treatable, and is not an inevitable consequence of aging.

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### What causes Erectile Dysfunction?

For years impotence was rarely mentioned or discussed. It was commonly believed to be due to psychological problems and treatment remained in the hands of the psychologists and psychiatrists. We know now that 80-90% of impotence is caused by physical problems, usually related to the blood supply of the penis .

There are three categories of causes

Psychogenic

Organic or physical

Neurological

**Premature Ejaculation**

**Premature Ejaculation** (PE) is the inability to maintain an erection long enough for mutual satisfaction.

**Premature ejaculation** is divided into a **primary** and a **secondary** form.

**Primary Premature Ejaculation**

**Primary** PE has been present since the patient first became sexually active. This patient has ALWAYS come too fast. The cause is often attributable to the element of haste in one's earliest sexual encounters.

This is learned behaviour, and like any learned behaviour it can be unlearned with the right help. This form of **primary** PE is psychogenic (as opposed to organic or physical) impotence.

Congenital Venous Leak

A subset of **primary** PE is those men born with congenital venous leak. The venous drainage system in the penis is not shutting down properly during arousal. The plug is loose in the drain in the bottom of the tub and the water runs out too fast. Many men in this group have never had a really hard erection. This is all fixable!

**Secondary Premature Ejaculation**

**Secondary premature ejaculation** means that after years of normal **ejaculation**, the duration of intercourse grows progressively shorter. Some men with severe PE will ejaculate during foreplay, even before penetration. This can be devastating. **Secondary** PE is due to physical causes, usually involving the penile arteries or veins or both.

Performance Anxiety

Another form of psychogenic impotence is performance anxiety. When you are stressed and anxious, erections may be difficult or impossible. Stress increases the body's production of catecholamines such as adrenaline and

nor-adrenaline, which are specific erection inhibitors. Learning to reduce your stress and anxiety levels under guidence will make it possible for you to produce long-lasting erections

Depression and Impotence

Depression is another cause of psychogenic impotence. Unfortunately, most anti-depressant medications themselves produce erectile failure, the last thing a depressed man needs.

Organic/Physical Impotence

By far, the most common cause of organic impotence, especially in older men, involves the penile arteries, the penile veins or both. When the problem is arterial, arteriosclerosis or hardening of the arteries is the usual culprit. Blunt trauma, sometimes from sports injuries, is a less frequent cause.

Impotence and Diabetes

Impotence is common in diabetics. Prolonged hyperglycaemia amongst many other processes also results in the thickening of capillaries, reducing blood and nutrient flow.

Lifestyle

The controllable risk factors for arteriosclerosis - overweight, lack of exercise, high cholesterol, cigarette smoking and high blood pressure - will produce erectile failure often before progressing to affect the heart. The coronary arteries (heart) are 1.5 - 2.0mm in diameter, the penile arteries are 0.6 - 0.7mm in diameter - 1/3 the size of the coronaries - and can become clogged sooner. Unless there is a change in lifestyle, coronary artery disease may follow impotence within a few years.

Neurologic Causes of Impotence

There are many neurological causes of impotence. Diabetes, as noted, chronic alcoholism, multiple sclerosis, heavy metal poisoning, spinal cord and nerve injuries, and nerve damage from pelvic operations such as prostatectomy can produce erectile dysfunction.

Drug-Induced Impotence

A great variety of prescription drugs such as blood pressure

medications, anti-anxiety and anti-depressant drugs, glaucoma eye drops, and cancer chemotherapy agents are some of the many drugs associated with impotence.

Hormone-Induced Impotence

Hormonal abnormalities such as increased prolactin (a hormone produced by the anterior pituitary gland), steroid abuse by body-builders, too much or too little thyroid hormone and hormones administered for prostate cancer may cause impotence. Rarely is low testosterone alone responsible for poor erections.

Sometimes congenital or acquired anatomic abnormalities prevent erections, such as Peyronie's Disease, an acquired curvature of the penis.

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**How are the causes diagnosed?**

The diagnosis of erectile dysfunction does not involve embarrassing and invasive testing.
The diagnosis of erectile dysfunction involves techniques such as taking a medical and sexual history, asking about smoking, alcohol and medications. Only a standard physical examination is usually needed, including taking your blood pressure. Laboratory tests on blood and urine will help identify any underlying medical cause that may need treatment.

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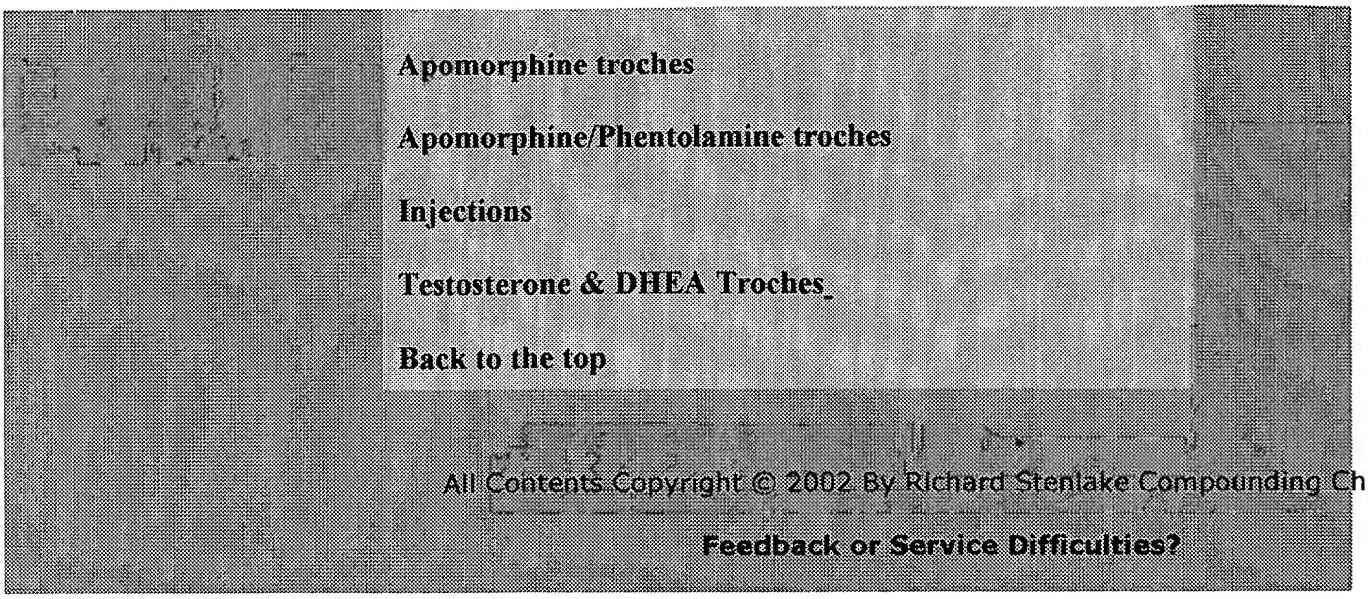
**Treatment for Impotence**

A man experiencing erectile dysfunction should seek medical attention. He should locate a Urologist or physician that specializes in impotence diagnosis and treatment.

No one form of treatment is right for everyone. Your doctor or specialist will advise on your best cause of remedy

Nearly always there are several treatment options. These include lifestyle modification, short-term intensive counseling, self-administered injection , prescription drug modification, correction of hormonal imbalance, and penile prosthesis implants.

Here at Stenlake compounding we prepare a variety of tailor made options that your doctor may prescribe.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## Causes of Impotence

***"The Cure Rate for Impotence is Approximately***

**We can not always eliminate the cause but we can cure the s For Example: " We can not cure Diabetes but we can sure cure the impot Diabetes causes!"**

---

Impotence or erectile dysfunction, is defined as failing to obtain and/or mainta erection satisfactory for intercourse more than 20% of the time. Every man strike once in a while, but if it occurs more than once out of every five times, there problem.

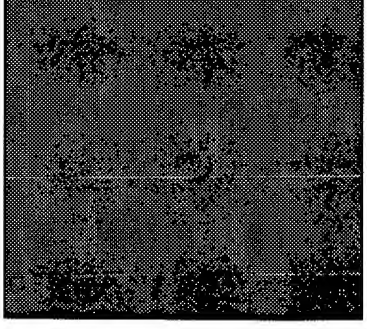
For years impotence was rarely mentioned or discussed. It was commonly believ be due to psychological problems and treatment remained in the hands o psychologists and psychiatrists. We know now that 80-90% of impotence is cause physical problems, usually related to the blood supply of the penis - the arteries veins which carry blood to and from the penis.

Every patient who comes to the Clinic has a psychological problem because he i functioning adequately as a male. But once the physical problem is fixed psychological problem usually goes away. For those men requiring psycholo counseling, the Clinic maintains a staff of highly qualified Psy. D. psychologists spe trained in sexual dysfunction.

A man has nowhere to hide. A woman can feign arousal and orgasm. But when a fails to obtain an erection or goes limp, the failure is obvious, humiliating frightening. But these problems are fixable! Sometimes the cause itself ca corrected. Other times the effects of problems will be corrected. We cannot example, cure diabetes. But we can cure the impotence the diabetes causes.

**Premature Ejaculation**
**Premature Ejaculation** (PE) is the inability to maintain an erection long enoug mutual satisfaction. How fast is too fast? If you think it's too fast, and your pa thinks it's too fast, then it's too fast. The average time of intercourse is around 10 minutes. If you are a skillful lover and bring your partner close to climax b penetration and within 45 seconds after penetration both partners climax, the seconds is not too fast. On the other hand, if you climax after 45 minutes wi arousing your partner, then 45 minutes is too fast!

Causes of Impotence
Treatment for Impotence
Prosthesis Implants
Peyronie's Disease
Enhancement Phalloplasty
Viagra
MSD Questionaire
Message of Hope (Video)
Penis Enlargement



arousing your partner, then 45 minutes is too fast!

**Premature ejaculation** is divided into a **primary** and a **secondary** form.

**Primary Premature Ejaculation**
**Primary** PE has been present since the patient first became sexually active. patient has ALWAYS come too fast. The cause is often attributable to the eleme haste in one's earliest sexual encounters. A boy matures sexually at age 13 -15 usually does not have a steady partner until several years later. These teen year when sexual drive and tensions are at their very peak. Nature's safety valve - noct emissions, or wet dreams - are not adequate to de-pressurize, so most young masturbate. When you masturbate, you have only yourself to please, so habituall ejaculate in one to two minutes. With repetition this "timetable" or schedule bec imprinted in your subconscious. The more frequently you masturbate, the more d the "rush" pattern becomes embedded. When you become older and finally do f partner, the same timetable calls the same old signals which now are not only us but harmful. You have another person to please besides yourself, and you can't. are, incidentally, other adolescent scenarios besides self-stimulation, all of which haste as their common denominator.

This is learned behavior, and like any learned behavior it can be unlearned, and w teach you a whole new set of signals. While you are practicing and mastering these skills, we will show you how to produce erections lasting 2 - 3 hours, often perm you to have 2 - 3 ejaculations before going flaccid. This form of **primary** psychogenic (as opposed to organic or physical) impotence.

**Congenital Venous Leak**
A subset of **primary** PE is those men born with congenital venous leak. The ve drainage system in the penis is not shutting down properly during arousal. The p loose in the drain in the bottom of the tub and the water runs out too fast. Many m this group have never had a really hard erection. This is all fixable!

If a small venous leak is present in your teens and twenties, your erections ma virtually normal, as long as your arteries remain flexible and can stretch with s arousal. As age progressively hardens and narrows the arteries, the faucet grad turns off and now the venous leak becomes apparent. You sense that you are abo lose your erection and you quickly ejaculate before it is too late. This is all correc sometimes with, but more often without, surgery.

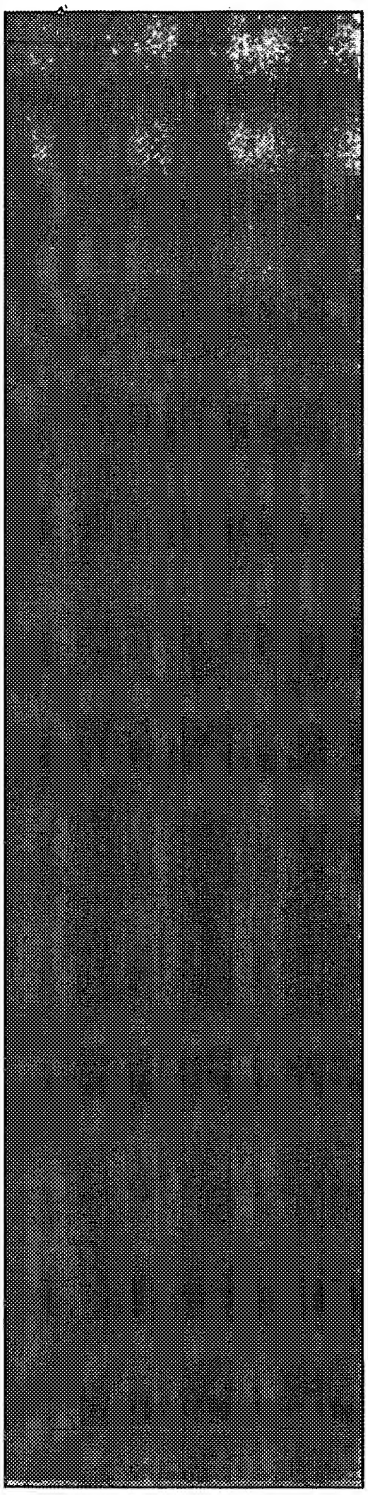
**The cure rate for PE approaches 100%.**

**Secondary Premature Ejaculation**
**Secondary premature ejaculation** means that after years of normal **ejaculation** duration of intercourse grows progressively shorter. Some men with severe PE ejaculate during foreplay, even before penetration. This can be devastating. **Secon** PE is due to physical causes, usually involving the penile arteries or veins or both.

**Performance Anxiety**
Another form of psychogenic impotence is performance anxiety. When you are str and anxious, erections may be difficult or impossible. Stress increases the b production of catecholamines such as adrenaline and nor-adrenaline, which are sp erection inhibitors. The therapists at the MSD Clinic will work with you br intensively, and effectively to teach you to reduce your stress levels and, at the time, we will make it possible for you to produce long-lasting erections while yo mastering these techniques. This, in turn, helps reduce stress by ensuring u long-lasting erections.

**Depression and Impotence**
Depression is another cause of psychogenic impotence. Unfortunately, anti-depressant medications themselves produce erectile failure, the last thi depressed man needs. Intensive counseling is the first line of defense here, helpe techniques that will provide usable erections. If quality psychotherapy is not effe or the patient cannot get along without his medications, a vacuum constriction de oral or self-injection therapy or the insertion of a penile prosthesis may be approp in selected cases.

**Organic Impotence**
By far, the most common cause of organic impotence, especially in older men, inv the penile arteries, the penile veins or both. When the problem is art arteriosclerosis or hardening of the arteries is the usual culprit. Blunt tra sometimes from sports injuries, is a less frequent cause. Many experts believe venous leak or "veno-occlusive incompetence" is the single most common vas



problem especially in younger men. Venous leak is a generally understood term can be likened to a loose plug in the bathtub drain. In a potent man, during s excitement, arterial inflow increases 5 to 8-fold and the penile drainage system c down, thus sustaining erections. When the drainage system fails to hold the blo the penis, the erection becomes soft and may fail.

**Impotence and Diabetes**
Impotence is common in diabetics. There are 9 million diabetic adult men in the and it is estimated that half are impotent and the other half will become impote time. The process involves **premature** and unusually severe hardening of the art Peripheral neuropathy, with involvement of the nerves controlling erections, is commonly in diabetics.

The controllable risk factors for arteriosclerosis - overweight, lack of exercise, cholesterol, cigarette smoking and high blood pressure - will produce erectile f often before progressing to affect the heart. The coronary arteries (heart) are 2.0mm in diameter; the penile arteries are 0.6 - 0.7mm in diameter - 1/3 the s the coronaries - and can become clogged sooner. Unless there is a change in life coronary artery disease may follow impotence within a few years. The MSD Clini work with you to prevent this.

**Neurologic Causes of Impotence**
There are many neurological causes of impotence. Diabetes, as noted, ch alcoholism, multiple sclerosis, heavy metal poisoning, spinal cord and nerve inj and nerve damage from pelvic operations such as prostatectomy can produce er dysfunction.

**Drug-Induced Impotence**
A great variety of prescription drugs such as blood pressure medications, anti-an and anti-depressant drugs, glaucoma eye drops, and cancer chemotherapy agent some of the many drugs associated with impotence.

**Hormone-Induced Impotence**
Hormonal abnormalities such as increased prolactin (a hormone produced by anterior pituitary gland), steroid abuse by body-builders, too much or too little th hormone and hormones administered for prostate cancer may cause impotence. R is low testosterone alone responsible for poor erections. Testosterone stimulates d but is believed to have little effect on erections.

Sometimes congenital or acquired anatomic abnormalities prevent erections, su Peyronie's Disease, an acquired curvature of the penis.

# VIVUS Announces Positive Results From TA-1790 Erectile Dysfunction Clinical Study

COMTEX News Network

MOUNTAIN VIEW, Calif., Nov 7, 2002 (BUSINESS WIRE) -- VIVUS, Inc. (Nasdaq NM: VVUS) today announced positive results of a clinical study designed to evaluate the safety and efficacy of TA-1790, its proprietary phosphodiesterase type 5 (PDE5) inhibitor, in men with erectile dysfunction (ED). This in-clinic trial, which utilized a RigiScan(R) device to measure penile rigidity in association with visual sexual stimulation, demonstrated that the peak efficacy response to TA-1790 was comparable to or greater than that observed with Viagra(R). Importantly, the peak penile response with TA-1790 occurred at the earliest time point evaluated in this study, 20-40 minutes after drug administration, as compared to the peak response to Viagra, which occurred 60-120 minutes after administration. Additionally, TA-1790 was well tolerated, with no indication of hypotension or visual disturbances.

"This double-blind, placebo-controlled in-clinic study demonstrated that TA-1790 is capable of restoring penile function in men with erectile dysfunction. The effects of TA-1790 were observed earlier than with Viagra, and the peak responses to TA-1790 were comparable to or better than those seen after treatment with a 50mg dose of Viagra," commented Dr. John Dietrich, VIVUS' Vice President of Research and Development. "This rapid onset of action was expected based on animal studies in which the maximum effect of TA-1790 was observed 15 minutes after administration," added Dr. Dietrich.

In addition to its rapid onset of action, in-vitro studies have demonstrated high specificity for the PDE5 enzyme. The following table presents the ratio of the amount of drug required to inhibit 50% of the activity of four important phosphodiesterase enzymes (PDE1, PDE3, PDE6 and PDE11) relative to each drug's inhibitory activity against PDE5. For example, it takes 8140 times as much TA-1790 to inhibit PDE1 as it does PDE5.

Fold Selectivity vs. PDE5

| | PDE1 | PDE3 | PDE5 | PDE6 | PDE11 |
|---|---|---|---|---|---|
| TA-1790(a) | 8140 | 22581 | 1 | 158 | 17900 |
| Tadalafil(b) | 4450 | 14800 | 1 | 187 | 5 |
| Sildenafil(b) | 80 | 4630 | 1 | 11 | 780 |

| | | | | | |
|---|---|---|---|---|---|
| Vardenafil(b) | 500 | 7140 | 1 | 25 | 1160 |

(a) Tanabe unpublished data

(b) Gbekor et.al. Journal of Urology Vol. 167.Abstract #967.2002

TA-1790's high specificity for PDE5 may predict a superior clinical safety profile. For example, preclinical studies have shown TA-1790 to have a substantially less blood pressure lowering effect than sildenafil in animals treated concomitantly with nitrates.

"TA-1790 has demonstrated a rapid onset of action, high specificity for PDE5 and a short plasma half life. We believe these characteristics are ideal for an on-demand treatment for ED," commented Dr. Dietrich.

VIVUS, Inc. is a pharmaceutical company engaged in the development of innovative therapies for the treatment of quality-of-life disorders in men and women, with a focus on sexual dysfunction. Current development programs target Female Sexual Dysfunction (FSD), Erectile Dysfunction (ED) and Premature Ejaculation (PE). The Company developed and markets in the U.S. MUSE(R) (alprostadil) and ACTIS(R), two innovations in the treatment of erectile dysfunction, and has partnered with Meda AB (Stockholm:MEDAa.ST) for the international marketing and distribution of its male transurethral ED products. In Canada, VIVUS has partnered exclusively with Paladin Labs (TSE: PLB) to market and distribute MUSE.

NOTE TO INVESTORS: VIVUS will hold a conference call to discuss results from TA-1790 erectile dysfunction clinical study today, November 7, 2002, beginning at 1:00 p.m. Eastern Time. You are invited to listen to this call (live or 14 days) via the Internet at the VIVUS website, WWW.VIVUS.COM.

Note to editors and investors: Additional written materials, recent releases and Company information are available through a variety of sources, including the VIVUS website WWW.VIVUS.COM and the VIVUS Fax-On-Demand Service 1-888-329-5719).

This news release contains forward-looking statements about the potential commercialization of products in treating male sexual dysfunction and reflects management's current beliefs. However, as with any pharmaceutical under development, there are significant risks in development, regulatory approval and commercialization of new products. There are no guarantees that future clinical studies discussed in this news release will be successful or that any product will receive regulatory approval for any indication. Further, even if the Company were to receive regulatory approval for a product, there could be no assurance that such a product would prove to be commercially successful. Please see the Company's filings with the Securities and Exchange Commission including, without limitation, the Company's Form 10-K and Forms 10-Q, which identify these and other risks and uncertainties that may cause actual results or events to differ materially from those described in this news release.

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**November 7, 2002 9:03am**
**Source: Business Wire**

**COMTEX End-User Agreement**

# VIVUS Announces Initiation of Premature Ejaculation Clinical Trial

COMTEX News Network

MOUNTAIN VIEW, Calif., Nov 20, 2002 (BUSINESS WIRE) -- VIVUS, Inc. (Nasdaq NM: VVUS) today announced it has initiated a clinical trial to evaluate the safety and efficacy of VI-0162, its proprietary, oral, on-demand treatment for premature ejaculation (PE). This study is an at-home, double-blinded, placebo controlled crossover design. The trial is expected to be completed during the second quarter of 2003.

"Premature ejaculation is a significant component of male sexual dysfunction. In a recent survey published in the New England Journal of Medicine, the number of men with premature ejaculation exceeded those with erectile dysfunction," commented Dr. John Dietrich, Vice President of Research and Development at VIVUS.

Today, there is no approved medical therapy for the treatment of PE, even though some experts believe PE patients constitute the largest subset of patients with sexual dysfunction.

VIVUS, Inc. is a pharmaceutical company engaged in the development of innovative therapies for the treatment of quality-of-life disorders in men and women, with a focus on sexual dysfunction. Current development programs target Female Sexual Dysfunction (FSD), Erectile Dysfunction (ED) and Premature Ejaculation (PE). The Company developed and markets in the U.S. MUSE(R) (alprostadil) and ACTIS(R), two innovations in the treatment of erectile dysfunction, and has partnered with Meda AB (Stockholm:MEDAa.ST) for the international marketing and distribution of its male transurethral ED products. In Canada, VIVUS has partnered exclusively with Paladin Labs (TSE: PLB) to market and distribute MUSE.

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**November 20, 2002 10:00am**
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**November 20, 2002 10:00am**
**Source: Business Wire**

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FOR IMMEDIATE RELEASE

# VIVUS ANNOUNCES POSITIVE RESULTS FROM TA-1790 ERECTILE DYSFUNCTION CLINICAL STUDY

MOUNTAIN VIEW, Calif. (November 7, 2002) VIVUS, Inc. (Nasdaq NM: VVUS) today announced positive results of a clinical study designed to evaluate the safety and efficacy of TA-1790, its proprietary phosphodiesterase type 5 ( PDE5 ) inhibitor, in men with erectile dysfunction (ED). This in-clinic trial, which utilized a RigiScan® device to measure penile rigidity in association with visual sexual stimulation, demonstrated that the peak efficacy response to TA-1790 was comparable to or greater than that observed with Viagra®. Importantly, the peak penile response with TA-1790 occurred at the earliest time point evaluated in this study, 20-40 minutes after drug administration, as compared to the peak response to Viagra, which occurred 60-120 minutes after administration. Additionally, TA-1790 was well tolerated, with no indication of hypotension or visual disturbances.

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